REMARKS

Entry of the foregoing amendments, and reexamination and reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. § 1.104 and § 1.112, and in light of the following remarks, are respectfully requested.

Amendments

Claims 1 and 45 has been amended to more particularly recite that claimed method is to ameliorate acne scarring, not the treatment of acne *per se*, and that the treatment with the MMP inhibitor (genistein and/or quercetin) is topical. Accordingly, dependent claims 31, 38, and 50 have been amended to recite that the addition of those compounds is to treat the acne. In addition, the claims have been renumbered as requested. Claims dependent on claim 24 (and claim 50, for example), have been amended to exclude the combination of quercetin and an antibacterial. The spelling of ketoconazole has been corrected. The dependent claims directed to the use of an "triazole" have been more properly amended to recite the use of a cytochrome P-450 inhibitor (*e.g.*, paragraph bridging pages 24 and 25). No new matter is added.

Rejections under 35 U.S.C. 102

Kelly et al.

Claims 22-23, 25-28, and 45-48 stand rejected as anticipated by this reference, which rejection is respectfully traversed.

As presently recited, the claims do not recite treating or curing of acne. Rather, as explained through the instant application, it has been discovered that acne-affected skin has more MMPs than unaffected skin. It is posited that MMPs cause scarring due to the cycling between normal skin and acne-affected skin, where the skin is damaged (by the *p. acnes* bacteria and the action of MMPs). The present invention is for inhibiting these MMPs and thereby reducing scarring. In fact, the present inventors have found that genistein has no effect on acne *per se*.

Kelly et al. require a mixture of isoflavones to "improve[]" the "condition, colour, and general appearance" of acne within a couple of weeks. Applicants make no claim to treating acne by the application of genistein or quercetin.

Further, Kelly et al. do not appear to appreciate that acne often spontaneously resolves, and thereafter can reappear. For example, there is no follow-up with either patient mentioned in example 7 of Kelly et al. to determine if the acne re-appeared. Similarly important from a scientific point of view, there is no control in any of the Kelly et al. examples.

Also importantly, it appears that in the second part of Kelly's example 7 the *patient* and not the physician reported the improvement ("he reported a dramatic improvement in his acne"). This is anecdotal and not scientific evidence.

So one is left to guess whether the two clinical anecdotes in the reference were the only successes out of many failures, and the second success was apparently only self-reported.

In contrast, Applicants have explained in their specification a scientific basis for the present claims, based on *in vivo* clinical and histological evaluation, and not mere anecdotes.

Nevertheless, to further distinguish the claimed invention, the claim recitation has been amended to require the topical application of genistein or quercetin (although the active ingredient may be administered orally). All of the Kelly et al. examples require oral administration of a soy extract, not topical administration of one or two specific compounds.

Kelly et al. show no appreciation for acne scarring or the presence of MMPs in and near the acne lesion that contribute to scarring. In fact, the number of conditions supposedly able to be treated by Kelly is remarkable, given that no double blind or control is provided in any of their examples. Without any histological, physiological, or objective clinical data, Kelly et al. is not an anticipatory reference because one of ordinary skill in the art, given only anecdotal evidence of efficacy, is not placed in possession of the claimed invention. *See, e.g., In re Spada*, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). Accordingly, the claims as now amended are not anticipated, and would not have been obvious, from this reference.

Yamada et al.

Claims 22, 24, and 45 stand rejected as anticipated by this reference, which rejection is respectfully traversed.

As mentioned in connection with the Kelly et al. reference, Applicants make no claim that genistein or quercetin is antimicrobial. Yamada *et al.* require as essential components an antibacterial that is rutin or a derivative, which both appear to be structurally related to quercetin given the structures shown in this reference. Rutin and quercetin are flavonols; genistein is an isoflavone. Note that the abstract cited shows the structures of all the Yamada *et al.* compounds.

Unlike Kelly et al., Yamada et al. provide no specific reason why quercetin was present. It is understood why the antibacterial compounds are present. Submitted is an abstract obtained from NLM's Pub-Med[1] explaining that antibacterial properties of flavonoids against certain bacteria are enhanced when in combination.

The present claims rejected over this reference are self-sufficient in requiring only quercetin to prevent scarring. The use of solely quercetin is not described the reference. Like Kelly *et al.*, Yamada *et al.* (at least in the abstract cited) say nothing of acne scarring or the presence of MMPs.

The dependent claims have been amended to exclude the combination of quercetin and an antibacterial.

Accordingly, this rejection should now be withdrawn.

Burger et al.

Claims 22, 24-25, 29, 38-39, 44, 45-48, and 50 stand rejected over this reference, which rejection is respectfully traversed.

Column two (lines 40-43; emphases added) specifically states that the use of a flavinoid (*e.g.,* genistein or quercetin) has "no or little effect on improving skin benefit[s] when used alone; a substantial increase in skin benefit is only realized when the flavonoid is combined with retinol or a retinyl ester." Thus, consistent

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[1] Biosci Biotechnol Biochem, 2002 May; 66(5); 1009-14; Arima *et al.*

with the previous argument over the Yamada *et al.* rejection, the art does not teach the use of genistein or quercetin alone.

The Burger et al. invention is based on the "discovery of a synergistic interaction between retinol or a retinyl ester and the specific flavonoid." (*Id.* at lines 44-45.) Therefore, the present independent claims are not anticipated, and would not have been obvious over this reference because the genistein or quercetin alone is stated to have no benefit.

The present inventors have an allowed application (10/085,978) in which compounds including and similar to genistein and quercetin are use to *prevent* hyperproliferation when retinoids are used. That is, retinoids activate the EGFR (epidermal growth factor receptor), which causes skin cell proliferation, and a compound such as (or like) genistein can prevent that hyperproliferation; the excessive growth can cause redness and other side effects that cause patients to stop using topical retinoid therapy. On the other hand, Burger *et al.* allege that they are preventing keratinocytes (KCs), a type of skin cell, from differentiating after proliferation.

Submitted herewith is an abstract of an article published in 1992 by some of the present inventors (*J. Invest. Dermatol.* 1992 Sep; 99(3):283-8; abstract also obtained from PubMed) explaining that retinoic acid therapy *in vivo* increases transglutaminase activity. In contrast, Burger et al. state that the enzyme activity is decreased (*e.g.*, column nine, first paragraph). Briefly, as understood by the undersigned, as KCs (keratinocytes) differentiate the TG1 enzyme discussed in Burger et al. acts to cross-link soluble and membrane proteins in the KCs, and this cross-linked "envelope" ends up on the surface of the skin as part of the *stratum corneum* (the outer, hard, dead skin cell part). The skin surface has been analogized to bricks (the cross-linked envelope) and mortar (lipid materials), and it is this structure that provides the skin's barrier layer; *in vitro* soap will dissolve cell membranes, but obviously *in vivo* soap does not dissolve skin. Accordingly, the assumptions by Burger *et al.* as to the effects of retinoids and certain flavonoids are incorrect in the real world; as stated at the end of the Griffiths et al. abstract, "certain aspects of keratinocyte terminal differentiation that are altered

in vitro by retinoic acid do not occur in vivo in human skin." Therefore, the present invention is not anticipated or rendered obvious by Burger et al.

Rejection under 35 U.S.C. 103

The rejection of claims 30, 31, 32, and 37 as obvious over the combination of Burger *et al.* and Kelly *et al.* is respectfully traversed.

As noted above, both of these references are silent, and do not appreciate, that MMPs are present in acne-affected skin and thereby contribute to acne scarring.

Burger *et al.* appear to appreciate that there are many flavonoids but, contrary to the allegation in the rejection, teach that only specific ones, namely quercetin and naringenin, will function in their invention. Col. 1, ln. 34-37; col. 2, ln. 11-13 and 44-45. Therefore, Burger et al. specifically teach away from substituting genistein for quercetin as alleged in the rejection. While Applicants stated that the compounds are equivalent for the purpose of this invention, Burger *et al.* clearly do not teach their equivance for the purpose of that invention.

As noted above, the claims have been amended to require a topical administration, thereby distinguishing Kelly et al. According, while it might have been obvious for Kelly to use quercetin or naringenin in their mixture of soy derivatives for oral administration, it would not have been obvious from this combination of references to use genistein or quercetin topically and to use another active ingredient, administered by any means. The Kelly *et al.* Example 7 teaches that no traditional active ingredient is needed because their extract mixture alone was sufficient to cure the acne. The Burger *et al.* science is wrong for *in vivo* effects and should be dismissed. Yamada *et al.* teach that quercetin must be combined with rutin antibacterial.

Thus, the combination of references does not teach the topical use of a combination of genistein and an active ingredient, such as a retinoid.

Conclusion

None of the references anticipates or renders obvious the topical use of genistein, quercetin, or a combination thereof as sufficient in itself to reduce acne scarring, as recited in the independent claims, and so the dependent claims are also allowable.

Respectfully submitted,

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